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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/690,495	10/21/2003	Arthur M. Krieg	C1039.70083US00	8657

7590 03/27/2007

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EXAMINER	
ARCHIE, NINA	
ART UNIT	PAPER NUMBER
1645	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/27/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/690,495	KRIEG ET AL.	
	Examiner	Art Unit	
	Nina A. Archie	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 January 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *52-77* is/are pending in the application.

4a) Of the above claim(s) *57 and 65-77* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *52-56 and 58-64* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *See Continuation Sheet*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Continuation of Attachment(s) 3). Information Disclosure Statement(s) (PTO/SB/08), Paper No(s)/Mail Date :2/26/2004, 2/17/2005, 3/16/2005, 12/20/2005, 2/07/2007.

DETAILED ACTION

Priority

Applicant's claim for domestic priority under 35 U.S.C. 119(e) is acknowledged.

Information Disclosure Statement

The information disclosure statements filed on 2/26/2004, 2/17/2005, 3/16/2005, 12/20/2005, and 2/07/2007 have been considered. Initialed copies are enclosed.

Election/Restrictions

Applicant's election of Group I claims 52-64 are acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 57 and 65-77 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected Group II (claims 65-77) or a nonelected species (claim 57), there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in reply filed on 1/29/2007.

Claim Objections

Claims 64 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. Claim 64 is drawn to a composition of claim 52, wherein the composition activates a non-specific immune response when administered by an intravenous or intraperitoneal route which does not further limit the structure of the composition of in claim 52.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claim 54 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claim recites the phrase "wherein the CpG is not a part of a palindromic sequence". Although Applicant filed an explanation in the Applicants Arguments/Remarks on 2/17/2005 of a CpG that is not part of palimdromic sequence, which activates a non-specific immune response in a subject, the specification states that disruption of the palindrome eliminated stimulation (see pg. 13, lines 36-38). The conception of the new subgenus "not part of a palindrome sequence" is not conveyed by this passage discussed above. Therefore it is not clear if the claim or specification give the CpG that does not have part of a palimdromic sequence the function of activating a non-specific immune response in a subject. This is a new matter rejection.

Claim 54 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling a composition for activating a non-specific immune response in a subject comprising an immunostimulatory CpG oligonucleotide (ODN 1, 1a, 1d, 2d, 3Dd, 3df, and 3Md and 4) does not provide enablement for composition

wherein a CpG is not part of a palindromic sequence. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the claimed invention.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is "undue." These factors include, but are not limited to:

(A) The breadth of the claims;
(B)The nature of the invention;
(C)The state of the prior art;
(D)The level of one of ordinary skill;
(E)The level of predictability in the art;
(F)The amount of direction provided by the inventor;
(G)The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

The breadth of the claims. The claims are drawn to a composition wherein the immunostimulatory CpG oligonucleotide is not part of palindrome sequence. The quantity of experimentation required to practice the invention as claimed would require the determination of accessible target sites, modes of delivery and formulations that encompass an immunostimulatory CpG oligonucleotide that is not part of palindrome sequence that functions as an antigen an elicits a non-specific immune response to produce antibodies and target specialized cells and/or tissues in any and/or all organisms/subjects, and further whereby treatment effects are provided for the claimed for immunostimulatory CpG oligonucleotide. Since the specification fails to provide

particular guidance for a composition wherein the immunostimulatory CpG oligonucleotide is not part of palindrome sequence it would require undue experimentation to practice the invention over the scope as presently claimed.

Nature of the invention. The claims are drawn to a composition for activating a non-specific immune response in a subject wherein the immunostimulatory CpG oligonucleotide is not part of palindrome sequence. The specification discloses immunostimulatory CpG oligonucleotide stimulation of B cells (pg. 14 Table 1). The application further indicates an induction of IL-6 and natural killer cells production in non-diseased mice after an intraperitoneal injection of unmethylated CpG containing oligos. The specification discloses in vitro using immunostimulatory CpG oligonucleotides (CpG ODN 1, 1a, 3Dd, and 4) in saline or PBS (see pgs. 17-18 and pgs. 25-27 Examples 1-4, 6, 7). The specification discloses in vivo methods administering immunostimulatory oligonucleotides (CpG ODN 1a, 1d, and 3db) in saline or PBS to mice (see pgs. 17-18 and pg. 27 Examples 5 and 8-12). The specification discloses production of IgM, natural killer cells, and IL-6 by administering specific oligos containing a CpG DNA segments in a murine model see (see example 1-7 pgs. 25-27).

The state of the prior art. The state of the art is show in vitro and in vivo studies that indicate that immunostimulatory CpG oligonucleotide that activate a non-specific immune response. The art shows that 1 or more palindrome sequences induce interferon-alpha and gamma, and enhance natural killer activity. The art also shows that the strongest activity are among extra-palindromic sequences (Kuramato et al 1992 Jpn. J. Cancer Res. Vol. 83, 1128-1131 see pgs. 1128-1131 in its entirety, Yamamoto et al 1992 Microbiol. Immunol. Vol. 36 No. 9 pg. 992 paragraph 3, pg. 993 last paragraph, pg. 994 paragraph 1, pg. 995). Furthermore the art shows that particular palindrome sequences for the immunostimulatory activity of oligonucleotides. The art indicates that oligonucleotides that do not possess a palindrome sequences do not stimulate spleen cells to produce interferon alpha and gamma and natural killer cell

activity (see Tokunaga et al 1992 Microbiol. Immunol. Vol. 36 No. 1, pgs. 55, pgs. 60, 61 paragraph 2 pg. 64)

The state of the art questions if all CpG oligonucleotide activate lymphocytes (see Branda et al 1996 Journal of Laboratory and Clinical Medicine pgs 335 Table 1, pg. 336 column 2). Therefore, the state of the art shows that immunostimulatory CpG containing oligonucleotide that have a palindrome sequence induce interferon-alpha and gamma, and enhance natural killer activity thus a non-specific immune response. For the reasons set forth supra, the state of the art show that the palindromic sequences activate a non-specific immune response. Furthermore the art has not shown an immunostimulatory CpG containing oligonucleotide that does not have a portion of a palindrome sequence that activates a non-specific immune response.

Guidance in the specification. The specification refers generally to an in vivo and in vitro of administering a composition of an immunostimulatory CpG containing oligonucleotide, which have the palindrome sequence to stimulate a non-specific immune response. The specification does not give an example of an immunostimulartory containing CpG that does not have a part of a palindrome sequence administered to a subject to activate a non-specific immune response. The specification as filed fails to provide particular guidance of the stimulatory effects of an immunostimulatory CpG containing oligonucleotide that does not have a part of a palindrome sequence provided in vivo in any and/or all organisms upon administration via any route of oligonucleotides, and further whereby treatment effects are provided in any and/or all organisms.

Working examples. The specification provides sufficient working examples of particular immunostimulatory oligonucleotides, which have a part of a palindrome sequence (see pg. 13 lines 19-24, pgs. 14-15 Table 1, pg. 16 Table 2 and lines 14-19, pg. 17 last paragraph, pg. 18 Table 3 and lines 9-14) as set forth supra.

In conclusion, the claimed invention is not enabled for a composition wherein a CpG is not part of a palindromic sequence and useful for activating a non-specific immune response as claimed. The specification discloses a composition comprising an immunostimulatory CpG oligonucleotide that have a part palindrome sequence to stimulate B cells. The specification does not teach nor provide guidance of the stimulatory effects of an immunostimulatory CpG containing oligonucleotide that does not have a part of a palindrome sequence that have the requisite action. The state of the art shows that a palindrome sequence has a key role in the immunostimulatory effects of a CpG containing oligonucleotides administered to subjects to activate a non-specific immune response. As a result, for the reasons discussed above, it would require undue experimentation for one skilled in the art to use the claimed product for the use as recited in the preamble. Further the art indicates that the CpG lacking a palindrome would not function to "activate a non-specific immune response in a subject".

Claim 60, dependent claim are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

As to claim 60 recites the phrase "near". However, neither the claim nor the specification clearly defines nor sets forth the meaning or means to assess "near". "Near" has no art defined meaning with respect to a composition. Therefore, the skilled artisan would not be readily apprised of the metes and bounds of "near" nor how to assess such. It is unclear how to interpret how to interpret what is considered "near" and inasmuch as it is not a recognized term and not defined in the specification.

Claim Rejections - 35 USC § 102 and 103

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

(e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made

to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 52-61, 63-64 are rejected under 35 U.S.C. 102(e) as being anticipated by Hutcherson et al US Patent 5,723,335 March 3, 1998 (filed March 25, 1994).

The claims are drawn to a composition for activating a non-specific immune response in a subject comprising: an oligonucleotide delivery complex, wherein the oligonucleotide delivery complex contains an immunostimulatory CpG containing oligonucleotide associated with a lipid, wherein the lipid is a liposome, wherein the composition activates a systemic, non-specific immune response in the subject.

Hutcherson et al teach a composition for activating a non-specific immune response in a subject (see column 5 lines 40-67, column 6 lines 31-43, column 7 lines 55-67, column 10 lines 46-57) comprising: an oligonucleotide delivery complex, wherein the oligonucleotide delivery complex contains an immunostimulatory CpG containing oligonucleotide (see SEQ ID NOs. 1, 2, 3) associated with a lipid wherein the lipid is a liposome (column 8 lines 50-55). Hutcherson et al teach a composition, wherein the non-specific immune response comprises stimulating lymphocytes thus stimulating natural killer (NK) cell activity (see column lines 6 31-39, column 10 lines 58-67),

wherein the CpG includes a phosphate backbone modification is a phosphorothioate (see abstract, column 5 lines 40-59, column 8 lines 31-50), wherein the oligonucleotide is 8-100 nucleotides in length (see SEQ ID NOs. 1, 2, 3), wherein the oligonucleotide comprises the formula 5' X1X2CGX3X4 3' wherein C and G are unmethylated, Xl, X2, X3 and X4 are nucleotides and a GCG trinucleotide sequence is not present at or near the 5' or 3' termini (see SEQ ID NOs. 1, 2, 3). Hutcherson et al teach a composition comprising a pharmaceutically acceptable carrier (see column 7 lines 49-55), wherein the oligonucleotide is synthetic (see column 8 lines 32-41).

Regarding the recitation of a composition for "activating a non-specific immune response" when administered by an intravenous or intraperitoneal route (claim 64); said recitation is considered an intended use and thus is given no patentable weight on the composition. Therefore the claims are drawn to a composition comprising an oligonucleotide delivery complex.

Claim 62 is rejected under 103(a) as being unpatentable over Hutcherson et al US Patent 5,723,335 March 3, 1998 (filed March 25, 1994) in view of Felgner et al US Patent 5,703,055 December 30, 1997 (filed January, 26, 1994).

Hutcherson et al is relied upon as set forth supra. However, Hutcherson et al does not teach a composition wherein the oligonucleotide is encapsulated in the cationic liposome.

Felgner et al teach a composition wherein the oligonucleotide is encapsulated in the cationic liposome oligonucleotide (see abstract, column 8 lines 43-50, column 9 lines 24-31, column 22 lines 25-40, column 25 lines 63-65). Felgner et al teach a composition comprising an oligonucleotide and a pharmaceutically acceptable carrier (see column 4 lines 65-67, column 5 lines 1-4).

It would have been prima facie obvious at the time the invention was made to encapsulate an oligonucleotide into cationic liposome taught by Felgner et al and that liposomes enhance the uptake of oligonucleotides taught by Hutcherson et al because

Hutcherson et al and Felgner et al teaches a composition for activating a non-specific immune response comprising an oligonucleotide delivery complex.

Status of the Claims

No claims are allowed.

Claims 57 and 65-77 are withdrawn.

Claims 52-56 and 58-64 are rejected.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nina A. Archie whose telephone number is 571-272-9938. The examiner can normally be reached on Monday-Friday 8:30-5:00p.m..

If attempts to reach the examiner by telephone are unsuccessful, the examiner supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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GAU 1645
REM 3B31

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